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Radiotherapy for Meningiomas – Where Do We Stand and What's on the Horizon?

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Radiotherapy for Meningiomas – Where Do We Stand and What's on the Horizon?

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Radiotherapy for Meningiomas

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Abstract

Radiotherapy, including conventionally fractionated external beam radiation therapy, stereotactic radiosurgery, and fractionated stereotactic radiotherapy, is a cornerstone in the interdisciplinary management of meningiomas. Recent advances in radiation oncology and also in other fields, such as neuropathology and imaging, have various implications for meningioma radiotherapy. This review aims to summarize current and anticipated developments, as well as active clinical trials related to the use of radiotherapy for meningiomas. In imaging, positron emission tomography has proven valuable for assessing the spatial extension of meningiomas and may enhance target delineation, treatment response monitoring, and recurrence assessment after radiotherapy. Particle therapy, including protons and carbon ions, as well as stereotactic radiosurgery and radiotherapy, allow for conformal treatments that permit dose escalation in selected patients with high-grade meningiomas. Additionally, emerging integrated molecular and genetic classifications offer superior risk stratification and may refine patient selection for radiotherapy. However,

there is a paucity of active meningioma trials directly investigating or refining the use of radiotherapy. In summary, significant advances in functional imaging, molecular and genetic diagnostics, and radiation treatment techniques hold the potential to improve patient outcomes and to avoid over- and undertreatment. Collaborative efforts and further clinical trials are essential to optimize meningioma radiotherapy.

Introduction

Meningiomas are the most common primary intracranial tumors, accounting for up to 40% of all brain tumors [1]. They are typically slow-growing, and many can be cured with surgical resection alone. However, meningiomas are often located in areas that are difficult to access or completely resect [2, 3]. In addition, a proportion of tumors display distinct biological aggressiveness with the tendency of early or late recurrence, making radiation therapy, including conventionally fractionated external beam radiation therapy, stereotactic radiosurgery, and fractionated stereotactic radiotherapy, an important and central treatment modality in contemporary management [4]. The current EANO and NCCN guidelines recommend postoperative radiotherapy for subtotally resected grade 2 tumors, all grade 3 meningiomas and as the primary treatment in selected grade 1 tumors [5, 6]. Conventionally fractionated external beam radiation therapy and, in some cases, stereotactic radiosurgery and fractionated stereotactic radiotherapy, are used for the treatment of grade 2 and 3 tumors [4-8]. For grade 1 tumors, stereotactic techniques are preferred for small to medium-sized, well-defined meningiomas, especially when there is a reasonable distance from organs at risk [9]. For all other grade 1 meningiomas, conventionally fractionated treatments represent the historical and well-known standard [4-6]. Radiation therapy, including re-irradiation, is also used in the setting of recurrent

meningiomas, but treatment algorithms are less well-defined, with limited data available [5, 6, 10, 11].

The optimal radiotherapy technique for meningiomas is a continuous area of active investigation [5, 9, 12]. In addition, open questions remain about target delineation, dose, fractionation, treatment margins, response assessment, patient selection, and risk-adapted treatments. Recent developments in functional imaging, molecular neuropathology, and radiation techniques have the potential to refine meningioma radiotherapy [4]. This work aims to summarize the most notable current and anticipated developments and clinical trials in the field of meningioma, with a particular focus on the use of radiotherapy, including conventionally fractionated external beam radiation therapy, stereotactic radiosurgery, and fractionated stereotactic radiotherapy. The role of systemic treatments and radionuclide therapies is discussed in-depth elsewhere [13, 14].

Materials and Methods

The authors conducted a non-systematic literature review of articles and studies on radiotherapy for meningiomas, positron emission tomography (PET) imaging, particle therapy, dose escalation, molecular markers, risk stratification, radiosensitization, and combination treatments. Relevant databases and search tools, including Medline, Embase, and the Cochrane Library, were utilized, using various search terms, including “meningioma”, “atypical”, “malignant”, “radiotherapy”, “radiosurgery”, "PET”, “DOTATATE”, “DOTATOC”, “imaging”, “proton therapy”, “particle therapy”, “carbon ion”, “heavy ion”, “re-irradiation”, “dose escalation”, “molecular”, “gene expression”, “risk”, “DNA methylation”, “radiosensitization”, “radiosensitizer”, “radiation-induced”, and “combination therapy”. Articles were screened by title and abstract and selected based on their relevance to the

outlined topics of interest. The reference lists of articles were also reviewed to ensure a comprehensive search. Full texts of the selected articles were assessed, and relevant information was extracted for further review. Findings and future areas for improvement in meningioma radiotherapy were summarized (Figure 1, Supplementary File 1). To obtain information on current, completed, and planned clinical trials focusing on the use of radiotherapy for meningioma, a systematic search was conducted. No filters were applied, and all types of radiation therapy were considered, including conventionally fractionated radiotherapy, stereotactic radiosurgery, and fractionated stereotactic radiotherapy. ClinicalTrials.gov (253 studies), the EU Clinical Trials Register (11 studies), the International Standard Randomised Controlled Trial Number registry (ISRCTN) (11 studies), the Chinese Clinical Trial Registry (ChiCTR) (11 studies), the German Clinical Trial Registry (DRKS) (5 studies), and the Australian New Zealand Clinical Trials Registry (ANZCTR) (3 studies) were searched on August 15, 2024, yielding 294 results. A uniform search term ("meningioma") was utilized for five out of six study databases, while the German translation of the term was applied for the DRKS search ("Meningeom"). The 294 search results were then individually assessed for their objective and were included in the review if they investigated an intervention directly related to the use of radiotherapy in meningiomas (Figure 2). Relevant study information was then retrieved, analyzed, and summarized to provide a comprehensive overview of the current landscape of radiotherapy trials for meningiomas (Table 1). Figures were partially created with BioRender.com. Due to the nature of the work, no institutional review board approval was required.

Results

PET Imaging

Background and Target Delineation

Currently, meningioma imaging relies predominantly on magnetic resonance imaging (MRI) and computed tomography (CT). These modalities have limitations in meningiomas with complex geometry, osseous involvement, and skull base location [15-17]. Moreover, postoperative changes and scar tissue can reduce the sensitivity of MRI in detecting residual or recurring meningiomas. Therefore, functional imaging modalities such as PET are of particular interest for the detection and spatial assessment of meningiomas. ^{18}F-Fluorodeoxyglucose (FDG) PET imaging plays an insignificant role in meningioma imaging due to the rapid glucose metabolism in the healthy cerebral cortex and negligible uptake in the tumor [16]. Several recent studies have highlighted and underlined the advantages that somatostatin receptor (SSTR)-based PET offers for meningioma diagnostics [16]. SSTRs are highly expressed in meningiomas and, therefore, present an opportunity to be utilized to differentiate the tumor from its surrounding tissue [16, 18, 19]. Commonly used tracers exploiting the expression of SSTRs include gallium-68 (^{68}Ga)-DOTA-Tyr3-octreotide (^{68}Ga-DOTATOC), ^{68}Ga-DOTA-D-Phe1-Tyr3-octreotate (^{68}Ga-DOTATATE), and ^{68}Ga-DOTA-1-Nal3-octreotide (^{68}Ga-DOTANOC) [15]. SSTR tracer uptake also occurs in other diseases, such as pituitary tumors, Paget's disease, and chronic inflammation [15]. However, the uptake in meningiomas is usually higher, with a characteristic pattern and spatial distribution [15]. Therefore, additional PET imaging data can assist in accurate target delineation, which is the foundation for effective local therapies in general and especially for radiosurgery, given its high single doses and minimal treatment margins. This approach stands in contrast to conventionally fractionated radiotherapy with its larger margins and treatment volumes. The

benefit of an improved spatial target characterization is of particular importance for challenging target areas like the skull base, near the falx and superior sagittal sinus, and optic apparatus, where discrimination of healthy and tumor tissue can be difficult [15, 20, 21]. This also applies to the delineation and role of the dural tail, which remains a topic of debate [22, 23]. Potential thresholds of the PET signal may provide valuable guidance in difficult cases with reactive and ambiguous dural tail changes [21, 24, 25]. Finally, the postoperative setting, with its temporary and long-term anatomical changes, represents another challenging situation for an accurate target delineation.

The utility of PET imaging with the SSTR tracer ^{68}Ga-DOTATOC in refining the target volume delineation for stereotactic fractionated radiation therapy has already been described for years [26, 27]. ^{68}Ga-DOTATOC-PET data provide crucial information on the spatial extent of meningiomas, leading to significant target volume changes in 73% of patients in one study [27]. The authors of this study created treatment volumes for 26 intracranial meningiomas based on CT and MRI, PET alone, or a combination of all three. In 19 out of 26 cases, the target delineation was significantly modified based on the available PET data [27].

Moreover, the use of PET data not only helps with targeting the tumor more precisely but also with reducing the dose to organs at risk, such as the optic apparatus, brainstem, and hippocampi [28]. Subsequent studies by various other groups have supported these findings [26, 29-32]. Biological tracers presumably provide more accurate tumor definitions, which can lead to changes in target volumes but also reveal additional treatment targets. One example with additional targets is provided by Perlow and colleagues [31]. In this planning study, the additional value of PET imaging compared to MRI was investigated by 4 radiation oncologists and 3 neuroradiologists for 25 meningioma patients. While the median PET-based target volume for radiotherapy was smaller than the median MRI-based volume, PET

imaging revealed new nonadjacent tumor manifestations not visible on MRI in 7 cases (28%). These meningioma lesions likely would not have been considered during a typical MRI-only planning process.

While the changes in target delineation can be significant, as highlighted by the examples above, the true benefit must be evaluated in terms of local tumor control. The evidence is limited, but the tumor control appears at least similar when compared to MRI-based planning, with one study reporting superior outcomes with PET-based planning for low-grade meningiomas [33].

Given the lack of prospective randomized trials, the long-term benefit of PET imaging for radiotherapy target delineation remains an area of active investigation. For instance, it is unclear whether meaningful differences in the PET utility between benign and high-grade meningiomas exist [28]. As single meningioma cells can be found in dural tissue up to 3 cm from the macroscopic tumor, the sensitivity and negative predictive value of the PET signal for small deposits of residual tumor is not well-defined [23]. This is of particular importance for stereotactic radiosurgery and fractionated stereotactic radiotherapy, where smaller treatment margins are used.

Treatment Decision-Making

While target delineation is of utmost importance for radiotherapy treatment planning, PET imaging may also assist in other clinical scenarios, such as treatment decision-making. Reliably identifying sites of active and residual disease after surgery is essential to avoid over- and undertreatment [5]. Recently, data from a prospective single-center registry were published [34]. The authors used ^{68}Ga-DOTATATE PET-CT imaging in 60 meningioma patients at presentation to the department to inform further disease management, 50% of whom had recurrent disease at time of enrollment into the study. Out of the 60 analyzed patients,

48 received radiotherapy with an average dosage of 54 Gy, one patient underwent a second surgery, and 11 were observed. Only three patients (5%) experienced local failure, two of whom had PET-avid disease in their postoperative cavity but chose not to be treated. Furthermore, five patients with no local PET uptake were followed with observation, and none experienced disease recurrence. However, the limited duration of follow-up has to be considered and limits the ability to draw significant conclusions. Nevertheless, the reported data underline the potential value of PET-guided decision-making, also in determining the extent of surgical interventions in the case of cavernous sinus meningiomas or the necessity for adjuvant radiotherapy [35, 36]. In addition to these potential advantages, PET can better differentiate treatment effects from tumor progression compared to MRI and CT, facilitating earlier and more effective salvage treatments, such as re-irradiation, as highlighted by other analyses [15, 20, 21, 36, 37].

Outlook and Other Tracers

As all these benefits have been reported by multiple groups and institutions, the use of PET imaging for the management of meningiomas, particularly in the setting of radiotherapy, is expected to increase. Recent guideline recommendations also support this trend. For example, the RANO-PET group advocated for using SSTR PET in the detection of meningioma tissue, delineation of tumor extent for radiotherapy planning, and the diagnosis of tumor progression [15]. Moreover, the EANM/EANO/RANO/SNMMI joint practice guideline for the use of SSTR ligands in meningiomas embraces and underlines the widespread application of PET imaging in similar scenarios due to its various advantages over conventional imaging modalities, i.e., CT, MRI [38]. However, the available literature mostly consists of retrospective single-center analyses, highlighting the need for standardized, prospective studies to determine and confirm the presumed benefits in target delineation, risk

stratification, and disease detection [39]. Given the central role of radiotherapy in the management of meningioma patients, collective efforts are necessary to standardize PET-guided target delineation and to establish best practice standards in interpreting, leveraging, and applying PET data for radiotherapy. Finally, barriers to reimbursement for PET imaging and the availability of PET scanners need to be addressed to improve access for meningioma patients.

As nuclear medicine continues to advance, other tracers may also become relevant in the setting of PET-based radiotherapy for meningiomas. The emergence of ^{18}F-SiTATE, an ^{18}F-labeled SSTR targeting peptide, yields promising advantages over ^{68}Ga-labeled tracers. Initial reports on ^{18}F-SiTATE PET in meningioma patients suggest a tumor delineation with higher spatial resolution and simple tracer synthesis [16, 40, 41]. Other PET tracers, such as the pyrimidine analog 3'-deoxy-3'-(^{18}F)-fluorothymidine (FLT), also show interesting characteristics, e.g., better tumor-to-background contrast compared to FDG or helping to differentiate tumor grading [16, 42]. Available data also show that amino-acid-based PET can detect tumor areas for radiotherapy planning not visible on CT or MRI while improving the exclusion of healthy tissue [16, 43, 44]. FLT has shown the potential ability to identify aggressive meningiomas, as well as early tumor progression, with high accuracy, indicating that it might be helpful in the selection of high-risk patients after meningioma diagnosis [16, 42, 45]. Its clinical relevance in this setting, especially when compared to SSTR-based PET, will have to be studied further.

Particle Therapy

Background

Particle therapy, including proton and carbon ion therapy, has a long-standing history in the treatment of various intracranial tumors [46-50]. An increased treatment conformality and,

therefore, dose escalation can be achieved given its distinct dosimetric characteristics, characterized by a tunable Bragg peak, with little to moderate entry and negligible exit doses [49]. This results in a lower total integral dose to normal tissue compared to conventional photon radiotherapy [51, 52]. Moreover, proton therapy and carbon ions in particular, have a higher relative biological effectiveness (RBE) compared to photons, causing more complex DNA damage and, therefore, increased cell death [49, 53]. These advantages led to several studies and analyses investigating the role of particle therapy in the management of intracranial meningiomas [11].

Available Evidence and Outcomes

Today, there is a growing amount of data on the use of particle therapy for benign meningiomas, i.e., grade 1, with favorable local control rates and progression-free survival, frequently reported to be above 95% at 5 years [11, 54]. Moreover, proton therapy has been shown to preserve the quality of life of affected patients, highlighting its utility for the treatment of low-grade meningiomas [54]. However, the role of particle therapy in the management of grade 2 and 3 tumors is of particular interest given their distinct tendency to recur, causing significant morbidity and mortality [11, 54, 55]. A systematic review analyzing eleven studies with a total of 230 patients treated with particle therapy, primarily for World Health Organization (WHO) grade 2 and 3 meningiomas, suggested a local control benefit and survival advantage with a reduced risk of severe treatment-induced toxicity compared to conventional photon-based therapy [56]. However, significant limitations to these studies remain, such as the small sample sizes, varying and non-randomized patient selection, the heterogeneous cohorts analyzed, and retrospective study design.

While several prospective clinical trials are recruiting, the recent results of the single-arm phase 2 MARCIE trial for WHO grade 2 meningiomas helped to shed further light on the

efficacy of particle therapy, providing valuable insights into the application of carbon ion therapy [57]. This trial investigated the role of a bimodal radiotherapy approach, combining photon radiotherapy up to a dose of 50 Gy with a carbon ion boost of 18 Gy (RBE) with 3 Gy per fraction for tumors with subtotal resection, i.e., Simpson grade 4 or 5 [57, 58]. The 3-year progression-free survival and local progression-free survival rates of 80.3% and 86.7%, respectively, are higher than those observed in the RTOG 0539 trial [59]. The RTOG 0539, a non-randomized phase 2 trial investigating observation for low-risk meningiomas and fractionated radiotherapy with 54 and 60 Gy for intermediate- and high-risk meningiomas, demonstrated a 3-year progression-free survival of 72.7% in a comparable but small subgroup of 11 subtotally resected grade 2 tumors [59]. While acknowledging the limitations of cross-trial comparisons and the relatively small sample size of both cohorts (MARCIE 33 patients, RTOG 0539 51 patients in the high-risk subgroup evaluable for the primary endpoint analysis), the reported results mostly compare favorably to other photon-based analyses [55]. However, the increased biologically effective dose applied in the MARCIE trial should be considered and acknowledged, as the observed treatment effect might be primarily based on it. The role of dose escalation and its clinical implications will be discussed in the following section.

Recurrences and Re-irradiation

As many high-grade meningiomas will eventually recur, efficient and safe salvage therapies are required. The management of local recurrence is often driven by the local experience of managing physicians without the availability of high-level evidence, i.e., prospective clinical trials. Re-irradiation has emerged as one of the most rapidly evolving fields in radiation oncology, as highlighted by the recent consensus statement from ESTRO and EORTC, as well as the ongoing ReCare study within E²-RADIatE (NCT03818503) [60]. However, re-irradiation

is rarely standardized, underlining the necessity for respective guidelines and good practice recommendations concerning the treatment intervals, image registration, dose mapping of previous treatments, dose constraints for organs at risk, and fractionation [10, 60].

Re-irradiation for meningiomas utilizing particle therapy is a potential treatment option, with patient selection and minimization of treatment-associated toxicity remaining two of the key challenges in the field [11, 61, 62]. A recent analysis of 32 patients, including 22 grade 2 and 3 meningiomas, undergoing proton re-irradiation demonstrated a favorable 2-year progression-free survival rate of 74.5% [61]. The median progression-free survival for grade 2 and 3 tumors was 27.5 and 14.1 months, respectively. Notably, all patients underwent PET imaging before re-irradiation. Most of the treatment failures after re-irradiation occurred in-field (64%) and in-field and out-of-field (27%), with only a limited number of exclusive out-of-field tumor progressions (9%). These results compare well with another study of 42 patients receiving proton (8 patients) and carbon ion (34 patients) therapy [62]. The reported median progression-free survival for 31 high-grade meningiomas was 25.7 months, with more favorable outcomes observed in grade 2 tumors (median progression-free survival 34.3 months vs. 10.2 months for grade 3 meningiomas). Seventeen patients underwent PET imaging to guide target volume definition, and most treatment failures after re-irradiation occurred either within the field or at its border. Considering the nature and poor prognosis of recurring grade 2 and 3 tumors, these findings emphasize the potential efficacy of particle re-irradiation.

Treatment Toxicity

While these results are encouraging, there is a distinct need to balance treatment efficacy with potential toxicity. This is particularly important for particle therapy due to its increased biological effectiveness. Cases of high-grade radiation-induced necrosis, neurocognitive

decline, and brain injury are well documented, highlighting the need for diligent patient selection, treatment planning, and consideration of dose constraints [63, 64]. The MARCIE trial also provides insights into adverse events after heavy ion therapy. Fifteen of the 33 patients (45.4%) developed radiation-induced contrast enhancement, with nine patients (27.3%) presenting with neurological symptoms, including headache, dizziness, and sensory or motor deficits [57]. Notably, one patient died five months after the completion of treatment due to progressive radiation necrosis. This treatment-associated death led to the early termination of the trial, resulting in the cessation of recruitment after 33 of the initially targeted 40 patients. While our understanding of varying RBE and linear energy transfer continues to evolve, unanswered questions about the drivers and predictors of radiation-induced brain injury remain [63-66]. Radiation dose, treatment volume, and fractionation are just some of the prominent factors that influence the risk of radiation necrosis, with recent data highlighting the role of patient heterogeneity [64, 66]. Nevertheless, the superior physical properties of protons and carbon ions hold the potential to mitigate radiation side effects, with current data suggestive of fewer late complications like cognitive dysfunction, brain volume atrophy, cerebrovascular issues, and endocrinopathies [63].

As the technology for the delivery of particle therapy has also progressed through the years, starting with passive scattering techniques and leading to more advanced delivery methods such as pencil beam scanning with intensity-modulated proton therapy, it can be expected to see a further conformality increase of particle therapy [67]. One limitation continues to be the limited access to treatment facilities and resource intensity compared to photon-based radiotherapy [68]. Despite this potential, it has to be highlighted that most of the particle therapy toxicity and outcome data is derived from retrospective studies, with a notable risk of publication bias. This issue is aggravated by the use of different toxicity grading systems,

limited follow-up, and general heterogeneity of analyzed cohorts. Moreover, most studies investigating particle therapy lack head-to-head comparisons with patients treated with photon radiotherapy, highlighting the paucity of high-level evidence.

Outlook

International collaborative efforts are necessary to ultimately define the role of particle therapy in the treatment of meningiomas, particularly in the case of high-grade meningiomas. Given the relative rarity of grade 2 and 3 tumors, comprehensive and consequent reporting, ideally within the setting of prospective interventional and non-interventional studies, is of utmost importance to assess the treatment efficacy and acute and long-term toxicity of this radiation technique. The continuing lack of standardized, prospective, high-quality, and large-scale toxicity analyses calls for further studies to characterize and optimize the risk-benefit ratio. Finally, ongoing and future clinical studies must be accompanied by continuous physical and radiobiological research to guide patient selection and treatment delivery.

Radiation Dose Escalation

Available Evidence and Outcomes

Since the implementation of radiation in the treatment of solid malignancies, countless efforts have been undertaken to define the ideal dose for each tumor type and indication, maximizing tumor control rates with acceptable treatment-associated toxicity. This also applies to meningiomas. According to current guidelines, adjuvant radiotherapy for grade 1 meningiomas after gross total resection is not required [4, 5]. The local control rates after radiotherapy following subtotal resection or in the case of radiologically diagnosed benign lesions are high [9, 22]. Low-grade tumors do not seem to benefit from dose escalation and can be effectively and safely treated with fractionated radiotherapy with a dose of 54 Gy,

which can be reduced to 50.4 Gy near critical organs at risk [6, 69]. Stereotactic radiosurgery and fractionated stereotactic radiotherapy are well-established, time-saving, and effective treatment options for small and medium-sized grade 1 tumors and local recurrences [70, 71]. For stereotactic radiosurgery, i.e., single fraction treatments, doses often range from 12 to 16 Gy with frequently used prescription isodose lines between 50 and 80%, depending on the treatment platform [5, 6]. Prescription doses for fractionated stereotactic radiotherapy range from 25 to 30 Gy for five fractions [5, 6]. In high-grade meningiomas, i.e., grade 2 and 3 tumors, outcomes after radiotherapy are markedly inferior [59, 72-74]. Here, doses for the treatment typically range between 54 (grade 2 meningiomas after gross total resection) and 60 Gy (all other grade 2 and 3 tumors), while the preferred dose is at least 59.4 Gy [6]. Prescription doses in stereotactic radiosurgery mostly range from 16 to 20 Gy and from 21 to 35 Gy in the case of fractionated stereotactic radiotherapy with three to five fractions [5-7].

One potential way to improve local control could be the administration of higher doses, i.e., dose escalation, assuming an accurate target delineation and adequate treatment margins. Recent advancements in radiation technology, such as particle therapy, stereotactic radiosurgery, and fractionated stereotactic radiotherapy, which allow for a highly conformal dose distribution and improved sparing of organs at risk, suggest a feasible dose escalation to 70 Gy or more in select cases [6, 75]. Recent analyses provide more evidence of a benefit with higher doses [75].

Kim and colleagues reported on the dose-response relationship in 135 atypical meningiomas receiving photon-based postoperative radiotherapy [76]. A total of 73 patients, 54 with gross total resection, received a median equivalent dose in 2 Gy fractions (EQD2) of 60 Gy using an α/β ratio of 4 Gy. The median number of fractions was 34. The remaining patients underwent radiotherapy with a median EQD2 dose of nearly 55 Gy. The multivariable Cox

regression analysis utilizing a spline smoothing method revealed a continuously decreasing risk of local failure, disease progression, and overall survival with increasing radiotherapy doses [76]. Another study by Zeng and colleagues investigated the role of dose-escalated radiation therapy in 111 grade 2 and seven grade 3 meningiomas [77]. All 54 patients receiving a dose-escalation treatment with up to 70 Gy had residual disease. Dose escalation showed better outcomes in local control and progression-free survival in the multivariable Cox analysis, with a trend toward improved overall survival. Notably, there was no increased incidence of radiation necrosis in the high-dose group (two cases vs. five patients in the low-dose group). While these two studies on high-grade meningiomas were retrospective, Pontoriero and colleagues reported results from a prospective study involving 16 patients who were treated with dose escalation [78]. The study included patients with either subtotally resected or recurrent grade 2 meningiomas. The authors predominantly applied a combination of 46 Gy of intensity-modulated radiotherapy or volumetric-modulated arc therapy with a 15 Gy hypofractionated stereotactic radiotherapy boost in three fractions. The 3-year progression-free survival of patients with subtotal resection was 100% and 55.5% in recurrent tumors, with acceptable toxicity, i.e., no grade 3 adverse events. The favorable progression-free survival observed in the MARCIE trial applying a carbon ion boost in grade 2 tumors after subtotal resection has already been discussed in the previous section.

Outlook

All these results and a recent systematic review highlight the potential of dose escalation to improve outcomes in high-grade meningiomas [75]. As dose escalation strategies are hardly standardized, it is evident that highly conformal radiation techniques are required to maintain a favorable risk-benefit ratio. Particle therapy represents one option, but with the increasing availability, excellent conformality, and lower costs of stereotactic radiosurgery

and fractionated stereotactic radiotherapy, other options are also available. These alternatives potentially allow for broader and faster implementation. However, even with advanced radiation techniques, not all patients will be suitable candidates for an aggressive dose escalation if critical normal tissue dose constraints cannot be met. Careful patient selection and active strategies to reduce potential toxicity are crucial when assessing the efficacy of dose escalation strategies in high-grade meningiomas.

Two prospective studies plan to investigate the role of dose escalation with proton therapy (Table 1). For instance, NCT02693990 is a currently active phase I/II trial assessing the safety and utility of increased dose intensity-modulated proton therapy for high-grade meningiomas. The recruitment target of 22 patients is nearly reached, and the results are eagerly awaited to obtain more insights. However, further collaborative efforts will be necessary to provide more prospective data and determine the necessary margins, dose, and fractionation to improve patient outcomes after adjuvant and salvage treatments. Moreover, the ideal target definition of dose escalation and its delivery with simultaneous integrated or sequential boosts have to be investigated.

Molecular Risk Stratification

Combining Molecular Insights and Histopathology

The diagnosis of meningiomas has historically relied on light microscopy and immunohistochemical staining. The field of neuropathology, however, has undergone a revolution in the past years with considerable advances in molecular and genetic diagnostics [79]. While molecular and genetic markers such as the isocitrate dehydrogenase mutation and 1p/19q codeletion have significantly refined the classification and risk stratification of gliomas, comparable markers in meningiomas have been relatively limited until recently. DNA methylation analyses, copy number variations, and further multiomics techniques have

led to valuable insights into the biology and behavior of meningiomas [80, 81]. This progress is highlighted by the recent introduction of two molecular features into the grading assessment of the 2021 WHO Classification of Tumors of the Central Nervous System [79]. The homozygous deletion of CDKN2A/B or a TERT promoter mutation are, regardless of other histopathological or genetic characteristics of the tumor, sufficient to assign a grade 3 meningioma diagnosis [79]. Yet, this introduction is just the beginning as evidence has accumulated over the past years that the integration of molecular and morphologic tumor characteristics yields substantial advances in risk stratification and outcome prediction than just the WHO grading alone [81-88].

Available Evidence and Classifiers

For instance, an international multicenter analysis established an integrated risk classification incorporating WHO grading, specific copy number variations, namely 1p, 6q, or 14q losses, and DNA methylation profiles [86]. The final risk score with three risk groups (low, intermediate, high) had a superior accuracy in risk prediction compared to the WHO grading alone. These results can explain the well-known differences in meningioma aggressiveness and clinical courses despite similar WHO grading, and can help individualize treatment for affected patients. An example of the utility of methylation analysis and the value of specific copy number variations was provided by a post-hoc analysis of the EORTC 22042-26042 trial, which investigated the role of adjuvant radiotherapy for grade 2 and 3 meningiomas [72, 89]. The study retrospectively analyzed 53 of the 78 enrolled patients with next-generation sequencing and methylation profiling and determined 1p and 22q status. DNA methylation analysis, however, was only available in a subgroup of 38 patients. Nevertheless, the results underlined the independent prognostic role of methylation classes and 1p status, with patients assigned to the benign and intermediate methylation profile or

tumors with 1p loss had markedly worse progression-free survival than cases with benign methylation and an intact 1p [89].

Since radiotherapy is central to the adjuvant and salvage treatment of grade 2 and 3 tumors, a refined assessment can minimize the risk of both over- and undertreatment [90]. However, further efforts to refine patient selection for radiotherapy are of utmost importance. A recent international study analyzed 1856 meningiomas and developed a 34-gene expression risk score to predict treatment outcomes and response to radiotherapy [88]. The gene expression biomarker outperformed various other risk classification systems, including the 2021 WHO classification and integrated risk classification [86]. For the role of radiation therapy and improved patient selection, their finding of reliably predicting response after radiotherapy is especially noteworthy. The study incorporated cases from the RTOG 0539 trial, which prospectively investigated different treatment paradigms for histopathologically-defined low, intermediate, and high-risk meningiomas, further stratified by the surgical extent of resection [59, 91, 92]. By retrospectively applying the gene expression risk score and correlating it with patient outcomes, the authors found that postoperative management, e.g., adjuvant radiotherapy, could have been refined in nearly 30%. Moreover, the gene expression biomarker could identify tumors with an unfavorable prognosis benefitting from radiotherapy, while the results suggest that radiotherapy does not add a clinically meaningful advantage in favorable risk meningiomas [88]. Another recent work underlined the utility of molecular classifiers in guiding treatment decision-making [93].

Outlook

While these recent molecular studies have significantly changed our understanding and knowledge of meningioma biology, they yield the potential to refine the use of radiotherapy, ultimately introducing the concept of personalized radiotherapy in the field of meningioma

care. However, numerous molecular classifiers have been reported in the last five years [81]. Many utilize similar data, such as copy number variations or methylation profiles, but there is a distinct need for harmonization of classifiers. Moreover, other issues and challenges around affordability, technical standardization, and the required infrastructure to perform molecular risk stratification have to be addressed. While the field is rapidly evolving, future meningioma trials incorporating radiotherapy should implement these recent insights to improve patient selection, validate the actual utility of integrated molecular classifiers, and refine the necessary radiation doses and margins for molecularly homogenous tumors. Until then, a retrospective molecular workup for existing and completed radiotherapy trials is warranted and will provide further crucial data on the possibility of personalizing radiation oncology. The currently active EORTC-1308/ROAM and NRG-BN003 trials investigating the role of adjuvant radiotherapy in histopathologically-defined grade 2 meningiomas after gross total resection will provide further chances of molecular post-hoc analyses. Their results and subsequent molecular analyses may inform future trials in the field, leveraging the potential of improved molecular risk stratification for meningioma radiotherapy. Finally, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (c-IMPACT) will provide further recommendations on the proper use and interpretation of the available molecular and genetic data [94].

Other Areas

Radiosensitization and Combination Therapies

Improving the therapeutic ratio of radiotherapy is a long-lasting objective of radiobiological research. Drug-induced radiosensitization is one way to do so. While radiosensitizing drugs are used in other tumors, such as cisplatin in head and neck tumors, there is a lack of validated agents in the management of meningiomas. However, recent studies have

identified potential drug candidates, such as docetaxel, gemcitabine, valproic acid, and LB-100 [95-98]. Increasing the radiosensitivity, particularly of high-grade meningiomas, could allow for the application of sufficient radiation doses while preventing increased radiation-induced toxicities in the direct proximity of organs at risk. Yet, further prospective studies are indicated to translate the existing preclinical findings into the clinical management of patients. Finally, it must be acknowledged that the broader implementation and successful clinical validation of radiosensitizing drugs are exceptionally challenging, as highlighted by the paucity of success stories, particularly in brain tumors [99, 100].

Another approach to improve outcomes is the use of other combination treatments, not directly targeting radiosensitivity. For instance, the interplay of immunotherapy and radiation therapy is an active and evolving field of interest in many tumors, including meningioma [13, 101]. A recent phase 2 study investigating the programmed death-ligand 1 (PD-L1) inhibitor pembrolizumab in patients with recurrent and residual high-grade meningiomas showed promising results in a subset of tumors [102]. Consequently, there are several recruiting trials testing the efficacy of combining immunotherapy with radiotherapy in meningiomas, e.g., NCT03604978, NCT04659811, NCT02648997. Despite the lack of well-established systemic treatment options in meningiomas, recent preclinical and clinical data suggest that combination strategies can yield benefits in selected patients [13]. For instance, the role of mismatch repair deficiency in meningiomas has to be defined, given recent case reports demonstrating considerable responses after immune checkpoint inhibition [103, 104].

Considerations for Radiation-Induced and NF2-associated Meningiomas

While the vast majority of meningiomas grow *de novo*, a small proportion of tumors are radiation-induced or related to tumor syndromes such as neurofibromatosis type 2 (NF2), now referred to as NF2-related-schwannomatosis [105, 106]. Their differing ontogeny and discrepant behavior call for further refinements in their management, including radiotherapy. Thanks to the increased survival chances of childhood cancer patients, late sequelae such as radiation-induced meningiomas are becoming more prevalent. These meningiomas often occur in younger patients and regularly exhibit aggressive behavior, with features that lead to higher WHO grading and a greater tendency to recur, such as increased mitoses and atypical or anaplastic characteristics [105, 107]. While some studies on radiation therapy, particularly stereotactic radiosurgery, show favorable results mostly in low-grade tumors, the optimal management remains a matter of debate, with partial overlap in the unanswered questions surrounding re-irradiation [60, 107-109]. Further efforts to improve outcomes of radiation-induced meningiomas are necessary, including prospective registries, additional molecular and genetic analyses, and refinement of treatment algorithms.

Such challenges apply to NF2-associated meningiomas as well. Patients affected by NF2 have a predisposition for various central nervous system tumors, including meningiomas, ependymomas, and schwannomas [106]. The role of radiotherapy in the management of NF2-associated tumors is controversial, given the risk for malignant transformation, particularly in vestibular schwannomas [110]. While recent cohort studies suggest a low risk in NF2-related meningioma and favorable outcomes after stereotactic radiosurgery, a national study with long-term follow-up underlined the excessive risk of malignant transformation and progression after radiotherapy, predominantly in vestibular schwannomas [111-113]. As multiplicity is common in NF2 patients, one study of 74 patients

with at least one meningioma observed a mean of three meningiomas per patient, the use of radiotherapy has to be carefully evaluated, especially in children and adolescent patients who are often surgical candidates and live long enough to face radiation-induced sequelae [112-114]. Therefore, the management of specific meningioma patient subpopulations with radiotherapy calls for further research and refinements while addressing the existing challenges pertinent to the nature of the underlying diseases and their origin.

Clinical trials

After the exclusion of six duplicates, a total of 288 clinical studies were retrieved and screened. The majority included patients with other tumors besides meningiomas (174/288, 60.4%) (Figure 2). One hundred fourteen studies (114/288, 39.6%) were specifically designed for meningiomas, 79 with an interventional (79/114, 69.3%) and 35 with an observational design (35/114, 30.7%). Most of them investigated neurosurgical or surgery-associated procedures (21/114, 18.4%), imaging modalities (15/114, 13.2%), and other therapies (12/114, 10.5%). Nine studies (9/114, 7.9%) were radiotherapy-related but had a recruitment status other than “recruiting”, “not yet recruiting”, or “active, not recruiting”. Another three studies (3/114, 2.6%) investigated combined treatments, including radiotherapy. After the exclusion of studies not related to meningiomas, with radiotherapy-unrelated or non-exclusive radiotherapy interventions, as well as all radiotherapy studies that are not active, recruiting, or not yet recruiting, a total of ten studies (10/288, 3.5%) remained for further analyses. The majority include the use of proton therapy for the treatment of meningioma (6/10, 60.0%), with two investigating the role of dose escalation (2/10, 20.0%). Four trials aim to clarify the efficacy of adjuvant radiotherapy (4/10, 40.0%), most of them exclusively in grade 2 meningiomas (3/4, 75.0%). Four trials (4/10, 40.0%)

primarily assess neurocognitive aspects such as neurocognitive decline after radiotherapy and volumetric changes in organs at risk. Trial sponsors are mostly located in Europe (6/10, 60.0%), followed by the US (2/10, 20.0%) and Asia (2/10, 20.0%). Further study details are summarized in Figure 2.

In summary, 19 radiotherapy trials were identified, regardless of their recruitment status, accounting for a small proportion of studies focused exclusively on meningiomas (19/114, 16.7%). With the inclusion of combination treatments, including radiotherapy, the number rises to 22 (22/114, 19.3%). However, only ten of the dedicated radiotherapy studies are active or planned (10/19, 52.6%; 10/114, 8.8%). Most meningioma studies incorporated systemic and targeted therapies, immunotherapy, as well as radionuclide therapy, or were related to surgical and perioperative procedures (45/114, 39.5%). Biomarker, preclinical basic science, quality of life, and neurocognitive studies comprise a smaller set of studies (11/114, 9.6%).

Conclusion

Recent advances in imaging, neuropathology, and radiation techniques and modalities hold the promise to significantly refine the efficacy and safety of radiotherapy for patients treated for newly diagnosed and recurring meningiomas. Moreover, combination treatments could further improve the therapeutic ratio of radiation therapy. The future patient selection for treatment may be successfully individualized utilizing (epi)genetic and molecular information. Prospective validation must occur to properly implement and validate these innovations. Despite the central role of radiotherapy in the management of meningiomas, only a small number of active trials are investigating and refining its use. While the presented advances provide the potential to improve meningioma radiotherapy, the

treatment of meningiomas remains interdisciplinary and should be carried out at experienced centers to ensure a well-balanced, personalized patient care. Future collaborative efforts of all involved specialties are necessary to improve long-term outcomes.

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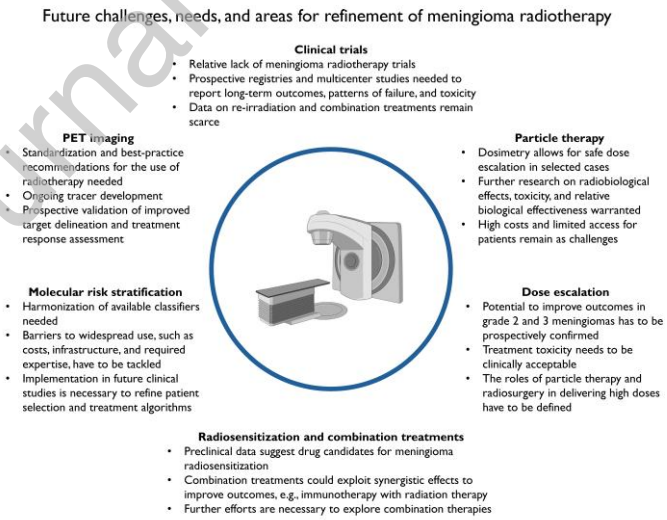

Figure 1. Overview of areas and challenges for the further refinement of meningioma radiotherapy.

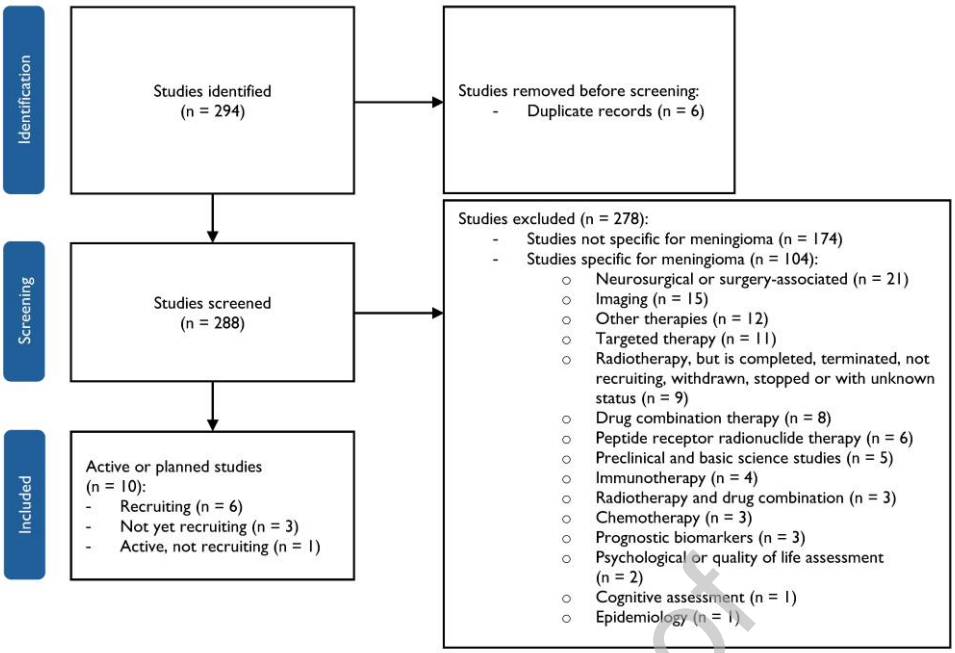

Figure 2. Search overview for active meningioma radiotherapy trials.

Table 1. Active and planned radiotherapy trials for meningioma.

Study description and objective	Primary endpoint	Sponsor	Trial status	Expected completion	Estimated enrollment (number of patients)	Trial identifier
Phase I/II trial investigating increased dose intensity modulated proton therapy for grade 2-3 meningiomas	Dose-limiting toxicity	Massachusetts General Hospital, US	Recruiting	2027	22	NCT02693990
Investigate dose escalation with proton radiotherapy for patients with atypical or anaplastic meningiomas	Progression-free survival	Technische Universität Dresden, Germany	Not yet recruiting	2029	90	NCT02978677
Investigate the impact of postoperative radiotherapy on outcomes in grade 2 and 3 meningiomas	Overall survival	University Hospital Montpellier, France	Recruiting[†]	2023	1204	NCT02973256
Phase III trial comparing observation vs. irradiation for gross totally resected grade 2 meningioma (NRG-BN003)	Progression-free survival	NRG Oncology, US	Recruiting	2027	148	NCT03180268
Investigate adjuvant radiotherapy for atypical meningioma without venous sinus invasion after gross-total resection	Progression-free survival	Second Affiliated Hospital, Zhejiang University, China	Not yet recruiting	2033	140	NCT04127760
Phase III trial comparing radiotherapy vs. observation in gross totally resected atypical meningioma (EORTC-1308/ROAM)	Disease-free survival	Walton Centre NHS Foundation Trust, UK	Active not recruiting[‡]	2026	157	ISRCTN71502099
Investigate advanced MRI in improving pre-selection of patients at risk for cognitive decline after radiotherapy	Correlation of cognitive failure and radiotherapy dose	Maastricht Radiation Oncology, Netherlands	Recruiting	2025	67	NCT04638478

(photon and proton treatments)						
Compare the impact of different modern radiotherapy techniques (photon and proton treatments) on cognition in grade 1-2 meningioma patients	Longitudinal changes in the volumes of organs at risk (hippocampus, amygdala, thalamus)	Chang Gung Memorial Hospital, Taiwan	Not yet recruiting	2026	74	NCT05832099
Compare the impact of different irradiation modalities (photon and proton treatments) on neurocognition in grade 1-2 skull base meningioma	Occurrence of cognitive impairment	Centre Francois Baclesse, France	Recruiting	2039	108	NCT06036706
Phase III trial comparing the cognitive and functional impact of proton therapy or modern fractionated radiotherapy in cavernous sinus grade 1 meningioma	Functional deterioration evaluated by neurocognitive test scores	Centre Francois Baclesse, France	Recruiting	2023	160	NCT05895344

†: ClinicalTrials.gov reports both an “unknown” and “recruiting” status.
‡: Recruitment completed.